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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/708,786	11/08/2000	Sudhir Agrawal	47508.700	2469

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WILMER CUTLER PICKERING HALE AND DORR LLP
60 STATE STREET
BOSTON, MA 02109

EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/708,786	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,6,8-11,14,15,17-20,23,24 and 26-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,8-11,14,15,17-20,23,24 and 26-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *October 18, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed October 18, 2004.

Claims 3, 4, 7, 12, 13, 16, 21, 22, and 25 have been canceled. Claims 1, 2, 5, 6, 10, 11, 14, 15, 19, 20, 23, and 24 have been amended. New claims 28-37 are acknowledged. Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, and 27-37 are pending in the instant application.

Claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, and 27-37 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed October 18, 2004 is acknowledged. The references referred to therein have been considered on the merits.

Specification

The amendment to the Specification to replace "CAMPOTOSAR" with the generic term "irinotecan" is acknowledged.

Claim Objections

In the previous Office Action mailed May 14, 2004, claim 10 was objected to because contained the word "the" twice in line 3. **This objection is withdrawn** in view of Applicants amendment to the claim to correct for this informality.

Claim Rejections - 35 USC § 112

In the previous Office Action mailed May 14, 2004, claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, and 27 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed May 14, 2004. **It is noted that new claims 28-37 are included in this rejection.**

Response to Arguments

In response to this rejection, Applicants argue that the term "statistically significant" is definite since the specification provides ample guidance regarding an acceptable method of determining statistical significance (i.e. an unpaired t-test). Applicants argue that a range of acceptable p values (i.e. from 0.08-0.0001) are provided in the Specification as filed. Applicants also argue that one in the art would understand how to select a method of determining statistical significance since those in the art routinely use statistical methods.

Applicant's arguments have been fully considered, but are not found persuasive because while the Specification provides guidance regarding an acceptable method of determining

statistical significance (i.e. an unpaired t-test), this statistical meter is not a requirement of the claim. Furthermore, the range of acceptable p values (i.e. from 0.08-0.0001) provided in the Specification as filed are not a requirement of the claim. The Examiner agrees that those in the art routinely use statistical methods, however, without a specific definition of what is "statistically significant", one of skill in the art is not apprised of the metes and bounds of the claim. For example, what values would be deemed "significant"?

In the previous Office Action mailed May 14, 2004, claims 1, 2, 5, 6, 8-11, 14, 15, 17-20, 23, 24, 26, and 27 were rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method for statistically potentiating the activity of CAMPOTOSAR® (irinotecan), the method comprising co-administering an oligonucleotide with CAMPOTOSAR®, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1, does not reasonably provide enablement for a method for statistically significantly potentiating the activity of a prodrug, the method comprising co-administering an oligonucleotide with the prodrug, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1. **This rejection is withdrawn** in view of Applicants amendment to the claims filed October 18, 2004. Specifically, Applicants amendment to the claims to recite "irinotecan" obviates this rejection.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed May 14, 2004, claims 1, 2, 5, 10, 11, 14, 19, 20, and 23 were rejected under 35 U.S.C. 102(b) as being anticipated by Koike et al. (Cancer Research, 1997 Vol. 57:5475-5479). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed May 14, 2004.

Response to Arguments

In response to this rejection, Applicants argue that all pending independent claims require co-administering an oligonucleotide with a prodrug. Applicants first argue that Koike et al. do not fulfill the requirement for anticipation of any of the pending claims because Koike et al. do not use an oligonucleotide. Applicants argue that the instant invention, at page 8, lines 23-27, provides a definition of an oligonucleotide as:

> Oligonucleotides in antisense embodiments are preferably from about 13 to about 100 nucleotides in length, more preferably from about 15 to about 50, and most preferably from about 15 to about 35. Oligonucleotides in non-antisense embodiments can be within these ranges, but can also preferably be from about 5 to about 15 nucleotides in length."

Applicants argue that Koike et al. teach an antisense cMOAT expression vector using an 805 bp fragment containing 77-bp of coding sequence and 35 bp of the 5'-noncoding fragment sequence. Applicants secondly argue that Koike et al. use a nucleic acid molecule that specifically targets a sequence while the claimed invention does not require the use of a specifically targeted oligonucleotide. Applicants thirdly argue that the pending claims specify that the oligonucleotide does not have two 5' or four 3' 2-O-methyl ribonucleosides and Koike et al. is silent on this issue.

Applicant's arguments have been fully considered, but are not found persuasive. Regarding Applicants first argument, the Examiner disagrees with Applicants contention that a definition of an oligonucleotide is provided in the instant specification at page 8, lines 23-27. While the instant specification at page 8, lines 23-27, discusses *preferred embodiments* of the claims, these embodiments are merely **preferred**, not **required**. It is noted that the instant specification does not provide a definition of an oligonucleotide. Therefore, given its broadest reasonable interpretation, the oligonucleotide of the instant claims can be any size, including the 805 bp fragment taught by Koike et al. Therefore, the disclosure of Koike et al. anticipates the instant invention.

Regarding Applicants second and third arguments, the Examiner agrees that Koike et al. use a nucleic acid molecule that specifically targets a sequence. Applicants argue that the claimed invention does not require the use of a specifically targeted oligonucleotide, however, this is not a requirement of the claims. For example, the claims do not require that the oligonucleotide not target a specific target. As broadly claimed, the oligonucleotide of the instant invention may target a sequence or may not target a sequence. Therefore, given its broadest reasonable interpretation, the disclosure of Koike et al. anticipates the instant invention. Finally, the pending claims specify that the oligonucleotide does not have two 5' or four 3' 2-O-methyl ribonucleosides. Koike et al. is teach the construction of the antisense cMOAT expression vector at pages 5475 and 5476. Koike et al. are specific regarding the fragment of the oligonucleotide and the subcloning of the oligonucleotide in an expression vector. However, Koike do not mention at pages 5475 or 5476, nor anywhere else in the article, that the antisense cMOAT does not have two 5' or four 3' 2-O-methyl ribonucleosides. Therefore, the Examiner is

interpreting that the antisense cMOAT does not have two 5' or four 3' 2-O-methyl ribonucleosides. Koike et al. are probably silent on this issue because the antisense cMOAT does not have two 5' or four 3' 2-O-methyl ribonucleosides.

Claim Rejections - 35 USC § 103

In the previous Office Action mailed May 14, 2004, claims 1-6, 8-15, 17-24, 26, and 27 were rejected under 35 U.S.C. 103(a) as being unpatentable over Koike et al. (Cancer Research, 1997 Vol. 57:5475-5479) in view of Baracchini et al. [U.S. Patent No. 5,801,154]. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed May 14, 2004. **It is noted that new claims 29-34 are included in this rejection.**

It is noted that in the previous Office Action mailed May 14, 2004, the application was indicated as naming joint inventors (see previous Office Action mailed May 14, 2004 at pages 10 and 11). This was an inadvertent error. **It is noted that this application does not name joint inventors.**

Response to Arguments

In response to this rejection, Applicants argue that Applicants argue that all pending independent claims require co-administering an oligonucleotide with a prodrug. Applicants first argue that Koike et al. do not fulfill the requirement for anticipation of any of the pending claims because Koike et al. do not use an oligonucleotide as defined by Applicants specification at page

8, lines 23-27. Applicants also argue that Baracchini et al. do not supply the deficiencies of Koike et al. because Baracchini et al. do not mention the use of a prodrug. Applicants further argue that the reference used in the rejection as evidence post-dates the instant application and thus would not supply a motivation to make the present invention (see Agrawal et al. (International Journal of Oncology, 2001 Vol. 18:1061-1069).

Applicant's arguments have been fully considered, but are not found persuasive because Applicant argues against the references individually, but must consider the rejection based upon the combination of the references. *See*, MPEP 2145. First, the Examiner disagrees with Applicants contention that a definition of an oligonucleotide is provided in the instant specification at page 8, lines 23-27. While the instant specification at page 8, lines 23-27, discusses *preferred embodiments* of the claims, these embodiments are merely **preferred**, not **required**. It is noted that the instant specification does not provide a definition of an oligonucleotide. Therefore, given its broadest reasonable interpretation, the oligonucleotide of the instant claims can be any size, including the 805 bp fragment taught by Koike et al. Second, Baracchini et al. was relied upon to provide motivation to the oligonucleotide of the instant invention, since Baracchini et al. taught modified oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Regarding the Agrawal et al. reference, the Examiner agrees that this reference post-dates Applicants invention, and thus would not supply a motivation to make the present invention. However, Baracchini et al. stands alone to provide enough motivation to modify the

oligonucleotide of the instant invention. Therefore the invention would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Applicant's amendment necessitated the new ground(s) of rejection presented below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 10, 19, and 35-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a written description rejection.**

Claims 1, 10, 19, and 35-37 are drawn to a method for statistically significantly potentiating the activity of a CPT-11 analog, the method comprising co-administering an oligonucleotide with the CPT-11 analog, wherein the oligonucleotide does not have two 5' and four 3' 2-0-methyribonucleosides, and wherein the oligonucleotide does not have the sequence of SEQ ID NO:1.

The specification provides examples for a method for statistically potentiating the activity of CPT-11 (irinotecan), the method comprising co-administering mdm-2 or HIV-1 specific oligonucleotides represented by SEQ ID NO:1 or SEQ ID NO:2, respectively. The specification

also provides an example for a method for statistically potentiating the activity of CPT-11, the method comprising co-administering an arbitrary oligonucleotide represented by SEQ ID NO:3. The art teaches a method for potentiating the activity of the prodrug, CPT-11, comprising co-administering a mismatch control oligonucleotide (see Wang et al., Clinical Cancer Research, 2001 Vol. 7:3613-3624). The art also teaches a method for potentiating the activity of the prodrug, CPT-11, comprising co-administering two protein kinase RI α subunit specific oligonucleotides (see Agrawal et al., International Journal of Oncology, 2001 Vol. 18:1061-1069). There are no examples provided in the instant specification for a method for statistically significantly potentiating the activity of a *CPT-11 analog*, comprising co-administering an oligonucleotide. The specification as filed does not provide sufficient description that would allow one of skill in the art to use CPT-11 to predict the physical property or chemical structure(s) of CPT-11 analogs, for example.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical

formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invention what is claimed." (See Vas-Cath at page 1116).

The skilled artisan cannot envision the detailed chemical structure(s) of the encompassed CPT-11 analogs. Applicant's specification only teaches CPT-11, but does not provide a sufficient number of representative species of the genus of CPT-11 analogs, which would allow one of skill in the art to predict the structures of all members of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed CPT-11 analogs in such full and concise terms so as to indicate that the Applicant had possession of the CPT-11 analogs at the time of filing of the instant invention. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (see page 1115).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
December 27, 2004

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600